TO STUDY THE COMBINED USE OF PLEURAL FLUID LYMPHOCYTE NEUTROPHIL RATIO AND ADENOSINE DEAMINASE FOR THE DIAGNOSIS OF TUBERCULOUS PLEURAL EFFUSION

DISSERTATION SUBMITTED FOR

MD DEGREE (BRANCH 1) GENERAL MEDICINE

APRIL 2017

THE TAMILNADU DR.M.G.R

MEDICAL UNIVERSITY

CHENNAI – TAMILNADU

CERTIFICATE FROM THE DEAN

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DECLARATION

I, **DR.R.SURESH,** solemnly declare that this dissertation titled "**TO STUDY THE COMBINED USE OF PLEURAL FLUID LYMPHOCYTE NEUTROPHIL RATIO AND ADENOSINE DEAMINASE FOR THE DIAGNOSIS OF TUBERCULOUS PLEURAL EFFUSION**" is a bonafide record of work done by me at the Department Of General Medicine, Government Rajaji Hospital, Madurai, under the guidance of **Dr.V.T.PREMKUMAR.M.D**, Professor, Department of General Medicine , Madurai Medical college , Madurai.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the rules and regulations for the award of M.D Degree General Medicine Branch- I; examination to be held in April 2017.

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ACKNOWLEDGEMENT

Above all I thank the Lord Almighty for His grace and guidance.

I wish to express my sincere thanks to our **Prof. DR.VAIRAMUTHURAJU. MD.,** Dean, Madurai Medical College and Government Rajaji Hospital, for permitting me to utilize the clinical materials from this hospital to conduct the study.

I wish to express my respect and sincere gratitude to my beloved teacher **Prof. Dr. V. T. PREMKUMAR,M.D.,** Head of the Department of Medicine, Government Rajaji Hospital, Madurai Medical College for his valuable guidance and encouragement during the study and also throughout my course period.

I would like to express my gratitude and sincere thanks to my beloved teacher, my guide and my Unit Chief **Prof. Dr. V.T.PREMKUMAR, M.D.,** for his valuable suggestions, patience, guidance and support throughout the study and also throughout my course period.

I am greatly indebted to my beloved Professors, **Dr. R. BALAJINATHAN, M.D., Dr. M. NATRAJAN, M.D., Dr. G. BAGYALAKSHMI,**

M.D.,DR.J.SANGUMANI.MD., Dr. C. DHARMARAJ, M.D., Dr.R.PRABHAKARAN, M.D., for their valuable suggestions throughout the course of the study.

I am extremely thankful to the Assistant Professors of Medicine of my Unit,, **DR.S.PEER MOHAMMED,M.D., Dr.K. MURALIDHARAN, M.D., and Dr.S.MURUGESAN,M.D.,** for their valid guidance, encouragement and suggestions.

I extend my sincere thanks to **Prof. Dr. PRABHAKARAN, M.D,** HOD Department of THORACIC MEDICINE , Government Rajaji Hospital and Madurai Medical College for his unstinted support and valuable guidance throughout the study period.

I am extremely thankful to **Prof. Dr. MUTHUKUMARESAN, MD.,** Head of the department of Bio-chemistry for their constant support, guidance, cooperation and to complete this study.

I am grateful to my family, collegues and friends who have encouraged me during my times of need. Their help and support have made this possible.

Finally, I thank all the patients, the most integral part of the work, who were always kind and cooperative. I pray for their speedy recovery, comfort and strength.

CONTENTS

INTRODUCTION

Pulmonary tuberculosis is the most frequent cause of death by an infectious agent worldwide. Among the extra pulmonary presentations after tuberculous lymphadenitis, pleural TB is the second most frequent Failure to diagnose and treat pleural TB can result in progressive disease with the involvement of other organs in as many as 65% of patients.

Conventional methods have proven to be insufficient for diagnosis of pleural TB. Direct examination of pleural fluid is inefficient because sensitivity is about

1%[1].Pleural fluid culture is more sensitive than direct examination but Mycobacterium tuberculosis requires 4 to 6 weeks to grow.

Many studies have demonstrated the diagnostic significance of increased adenosine deaminase (ADA) in tuberculous pleurisy, other studies have shown that ADA is of limited value[2],as raised levels are also associated with a number of other diseases including malignancies (especially those of hematologic origin), bacterial infections (Q-fever, brucellosis), empyemas, and collagen vascular diseases (including SLE and Rheumatoid arthritis).

Pleural effusions may arise secondary to pulmonary or systemic disease, and their development is classically associated with an influx of inflammatory cells into the pleural space. Lymphocytes predominate in malignant and tuberculous pleural effusions[3].

Hence this study is aimed to determine whether combined use of pleural fluid lymphocyte neutrophil ratio and ADA activity would provide a more efficient means for diagnosing tuberculous pleurisy than the use of ADA levels.

Pleural effusion is a very common clinical presentation of diseases. A correct diagnosis of the underlying disease is essential for the management of pleural effusion. A limited number of diseases causes transudative pleural effusions,

whereas exudative effusions require more extensive diagnostic investigations. Therefore, the first step is to classify them as transudates or exudates, even if this differentiation does not contribute to the etiological diagnosis.

Many criteria have been used to distinguish them, but none of them have been found to be satisfactory. Light's criteria is the most commonly used method

The criteria is one or more of the following for diagnosing exudates.

1.pleural fluid protein /serum protein >0.5

2.pleural fluid LDH/serum LDH >0.6

3.pleural fluid LDH more than 2/3 rd of the upper limit of serum.

It was found that even Light's criteria misclassified a large number of effusions , 25% of transudates as exudates.

AIMS AND OBJECTIVE

To determine whether the combined use of ADA activity and lymphocyte/neutrophil ratio would provide a more efficient means for diagnosing tuberculous pleural effusion than with the use of ADA alone.

REVIEW LITERATURE

Definition

The abnormal accumulation of fluid within the pleural cavity is defined as pleural effusion. The pleural space is the coupling system between the lung and the chest wall, and accordingly, it is a crucial feature of the breathing apparatus.

Pleural Fluid Formation

Fluid that enters the pleural space can originate in the

- pleural capillaries,
- the interstitial spaces of the lung,
- the intra - thoraciclymphatic's ,
- the intra - thoracic blood vessels, or
- the peritoneal cavity.

Pleural Capillaries

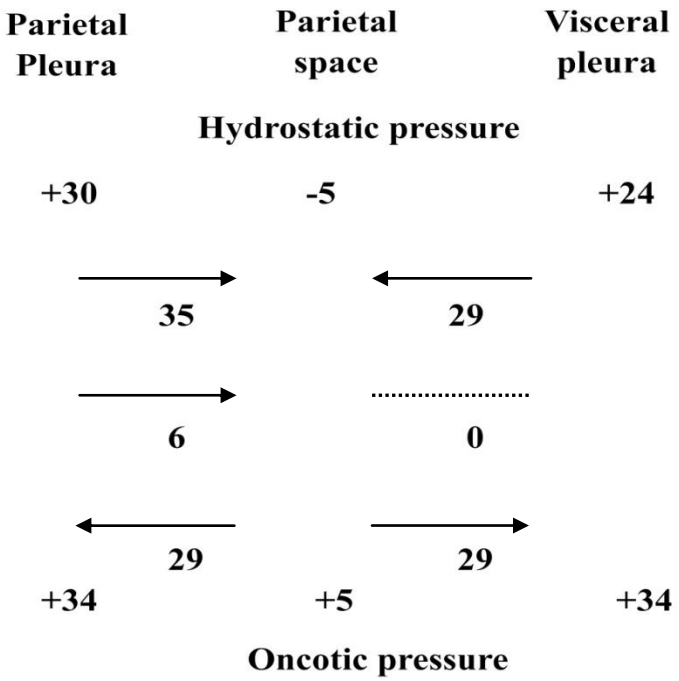
The movement of fluid between the pleural capillaries and the pleural space is believed to be governed by Starling's law of trans-capillary exchange.

The hydrostatic in the pleura is approximately 30 cm H_2O, whereas the pleural pressure is approximately -5 cm H_2O. The net hydrostatic pressure is therefore 30 -

(-5) = 35 cm H_2O and this favors the movement of fluid from the capillaries in the parietal pleura to the space. Opposing this hydrostatic pressure gradient is the oncotic pressure gradient in the plasma is approximately 34 cm H_2O. Normally, the small amount of pleural fluid contains a small amount of protein and has on oncotic pressure of approximately 5 cm H_2O, yielding a net oncotic pressure gradient of 34 -5 =29 cm H_2O. Thus, the net gradient is 35-29=6 cm H_2O, favoring the movement of fluid from the capillaries in the parietal pleura to the pleural space.

The net gradient for fluid movement across the visceral pleura in humans is probably close to zero, but this has not been demonstrated. The pressure in the visceral pleural capillaries is approximately 6cm H_2O less than that in the parietal pleural capillaries because the visceral pleural capillaries drain into the pulmonary veins. Because this is the only pressure that differs from those affecting fluid movement across the parietal pleura and because the net gradient for the parietal pleura is 6 cm H_2O, it follows that the net gradient for fluid movement across the visceral pleura is approximately zero. It is also likely that the filtration coefficient (L^p) for the visceral pleura is substantially less than that for the parietal pleura because the capillaries in the visceral pleura are much farther from the pleural space than those in the parietal pleura.

There appeared to be more fluid formation across the parietal pleura over the ribs compared with the intercostals spaces. In contrast, pleural liquid absorption was primarily in the parietal pleura adjacent to the intercostals space rather than in the parietal pleura overlying the ribs. There was also more fluid formation over the caudal ribs than over the cranial ribs. If the breathing frequency was increased, more fluid was formed.



Interstitial Origin

It has been demonstrated that the origin of much of the fluid that enters the pleural space, is the interstitial spaces of the lungs either high - pressure or high - permeability pulmonary edema can lead to the accumulation of pleural fluid. The amount of pleural fluid formed is directly related to the elevation in the wedge pressure. Increases in pleural fluid accumulation occur only after the development of pulmonary edema.

The pulmonary interstitial space is probably the origin of the pleural effusion in congestive heart failure patients.

It is likely that the origin of the pleural fluid with many conditions associated with lung injury, such as pulmonary embolization and lung transplantation, is also the interstitial spaces of the lung.

With increasing levels of interstitial fluid, it has been shown that the sub-pleural interstitial pressure increases. The barrier to the to the movement of fluid across the visceral pleura appears to be weak, even though the visceral pleura is thick. Therefore, once tha sub-pleural interstitial pressure increases, it follows that fluid will traverse the visceral pleura to the pleural space.

Peritoneal Cavity

Pleural fluid accumulation can occur if there is free fluid in the peritoneal cavity and if there are openings in the diaphragm. Under these conditions, the fluid will flow from the peritoneal space to the pleural space because the pressure in the pleural cavity is less than the pressure in the peritoneal cavity. The peritoneal cavity is the origin of the pleural fluid in hepatic hydrothorax, Meigs' syndrome and peritoneal dialysis.

Thoracic Duct or Blood vessel Disruption

If duct is disrupted, lymph will accumulate in the pleural space, producing a chylothorax. The rate of fluid accumulation with chylothorax can be more than 1,000 mL/day.

Origin of Normal Pleural Fluid

It is believed that the normally enters the pleural space originates in the capillaries in the pleura.

The amount of pleural fluid formed daily in a 50-kg individual would be approximately 15mL." The origin of the fluid does not appear to be the interstitial spaces of the lung because the protein level in the interstitial spaces is normally approximately 4.5g/dl, whereas the protein level in the normal pleural fluid is only approximately 1 to 1.5 g/dL, Higher vascular pressures should produce pleural

fluid with lower protein levels. Studies in rabbits with Evens blue dyed albumin have demonstrated that most fluid originates in the parietal pleura over the ribs.

Pleural Fluid Absorption

Lymphatic Clearance

Fluid clearance through the pleural lymphatic's is thought to explain the lack of fluid accumulation in normal individuals. The pleural space is in communication which the lymphatic vessels in the parietal pleura by means of stomas in the parietal pleura. No such stomas are present in the visceral pleura. Proteins, cells, and all other particulate matter are removed from the pleural space by these lymphatic's in the parietal pleura. The stomas through which the carbon particles exit the pleural space are in areas where the mesothelial cells are small and not flattened. Increased levels of nitric oxide in the pleura will cause these stoma to increase in diameter.

A 60-kg individual should have a lymphatic drainage from each pleural space on the order of 20mL/hr or 500 mL/day. The lymphatic's operate at maximum capacity once the volume of the pleural liquid exceed a certain threshold. The capacity for lymphatic clearance is 28 times as high as the normal rate of pleural fluid formation.

Clearance through Capillaries in Visceral Pleural

Until the mid - 1980's, it was thought that the primary rout for the exit of fluid from the pleural space was through the "capillaries in the visceral pleura in humans, almost all the pleural fluid is removed through the lymphatic's in the parietal pleura." Several hundred milliliters of water probably traverse the pleural membranes each day, but the net movement is of only a few millimeters because the osmolarity is nearly identical on each side of the membrane.

Alternative Mechanism for Pleural Fluid Removal

There is some evidence that transcytosis contributes to the removal of protein from the pleural space. Only 29% of the overall removal of albumin occurred through the stoma with small hydrothoraces, which 64% of the albumin from large hydrothoraces was removed through the stoma.

Pathogenesis of Pleural Effusions

Pleural fluid accumulates when the rate of the pleural fluid formation exceed the rate of pleural fluid absorption. Normally, a small amount (0.01 mL/kg/hour) of fluid constantly enters the pleural space from the capillaries in the parietal pleural. Almost all of this fluid is removed by the lymphatic's in the parietal pleura, which have a capacity to remove at least 0.20 mL/kg/hour. The lymphatic's remove the fluid exceeding the normal rate of fluid formation by a factor of 20.

General causes of Pleural effusions:

Increased pleural fluid formation

- Increased interstitial fluid in the lung –LVF ,pneumonia and pulmonary embolus
- Increased intravascular pressure in the pleura –RVF, LVF,superior venacaval syndrome
- Increased permeability of the capillaries in the pleura-pleural inflammation, increased level of VEGF
- Increased pleural fluid protein level
- Decreased pleural pressure-lung atelectasis, increased elastic recoil of the lung
- Increased fluid in peritoneal cavity-ascites, peritoneal dialysis
- Disruption of thoracic duct
- Disruption of blood vessels in thorax

Decreased pleural fluid absorption

- Obstruction of lymphatic in parietal pleura
- Elevation of systemic vascular pressure-superior vena caval syndrome ,RVF
- Disruption of the aquaporin system in the pleura

Increase Pleural Fluid Formation

Increased pleural fluid formation can occur when there is increased pulmonary interstitial fluid or when one of the terms in Starling's equation is changed such that more fluid is formed.

Increased Interstitial Fluid

The most common cause of increased pleural fluid formation is increased interstitial fluid in the lung. As mentioned earlier, whenever the amount of edema in the lung exceeds 5 g/gram of dry lung weight, pleural fluid accumulates, irrespective of whether the edema is due to high-protein or low-protein fluid. This appears to be the predominant mechanism for the accumulation of pleural effusions in congestive heart failure, parapneumonic effusions, acute respiratory distress syndrome, and in those who have undergone lung transplantation.

Increased Hydrostatic Pressure Gradient

If there is an increase in the gradient between the intravascular pressure and the pleural pressure, there will be an increase in the rate of pleural fluid formation through Starling's equation. Increases in the intravascular failure can occur with right ventricular failure, left ventricular failure, pericardial effusions, or superior vena cava syndrome. The most common situation producing a decrease in the pleural pressure is bronchial obstruction leading to atelectasis of the lower lobe or complete lung. A decrease in the pleural presser also occurs when the visceral pleura becomes coated with a collagenous peel and the lung becomes trapped. In these instances, the pleural pressure can become very negative (below -50cm H_2O).

Decreased pleural pressures can also contribute to pleural fluid accumulation in diseases in which the elastic recoil of the lung is increased.

Increased Capillary Permeability

Increased levels of vascular endothelial growth factor (VEGF) increase the permeability of the capillaries and may be at least partially responsible for the accumulation of pleural fluid. VEGF receptors have been demonstrated on mesothelial cells, and the levels of VEGF are higher in exudative effusions than in transudative pleural effusions. Of course, if the pleural surfaces become inflamed, the permeability of the capillaries may be increased.

Decreased Oncotic Pressure Gradient

Increased pleural fluid protein levels occur with increased-permeability pulmonary edema, hemothorax, and with conditions in which the permeability of the pleural capillaries is increased. This rate of fluid formation is approximately equal to the capacity of the lymphatic's to remove pleural fluid. Moreover, hypoproteinemia is thought to be a very uncommon cause of pleural effusion.

Presence of Free Peritoneal Fluid, or Disruption of the Thoracic Duct or an Intrathoracic Blood Vessel

If there is free fluid in the peritoneal cavity, it will lead to pleural fluid accumulation if there is a hole in the diaphragm. In a similar manner, chyle will accumulate in the pleural space if there is a disruption in the thoracic duct, and blood will accumulate in the pleural space if there is a disruption of a blood vessel in the thorax.

Decreased Pleural Fluid Absorption

Obstruction of Lymphatic's

The most common cause of a decrease in pleural fluid absorption is obstruction of the lymphatic's draining the parietal pleura. Normally, the lymphatic flow from the pleural space is approximately 0.01 mL/kg/hour or 15 mL/day because this is the amount of pleural fluid formed. However, the capacity of the lymphatic's is approximately 0.20 ml/kg/hour or 300 ml/day. Lymphatic blockade is an important factor that contributes to the development of a malignant pleural effusion.

Elevation of Systemic Venous Pressure

Because the lymphatic's drain into the systemic venous circulation, elevation of the pressures in the central veins decreases the lymphatic flow.

The pleural effusions developed because of (a) lymph leakage out of the lymphatic's that pass through the chest (these include the thoracic duct and the diaphragmatic and pulmonary lymphatic's); or (b) obstruction of lung or chest wall lymphatic's with subsequent leakage of interstitial fluid into the pleural space.

Clinical Manifestations

Normally, the pleural space contains only a few milliliters of pleural fluid. If fluid in the pleural space is detected on a radiologic examination, it is abnormal. Many conditions can be associated with pleural fluid accumulation. When pleural fluid is detected, an effort should be made to determine which of the many conditions.

Differential Diagnosis of Pleural Effusion

I. Transudative pleural effusions
    A. Congestive heart failure
    B. Cirrhosis
    C. Nephrotic syndrome
    D. Superior vena caval obstruction
    E. Fontan procedure
    F. Urinothorax

G. Peritoneal dialysis

H. Glomerulonephritis

I. Myxedema

J. Cerebrospinal fluid leaks to pleura

K. Hypoalbuminemia

L. Sarcoidosis

II. Exudative pleural effusions

A. Neo-plastic diseases

1. Metastatic disease
2. Mesothelioma
3. Body cavity lymphoma
4. Pyothorax-associated lymphoma

B. Infectious infections

1. Bacterial infections
2. Tuberculosis
3. Fungal infections
4. Parasitic infections
5. Viral infections

C. Pulmonary embolization

D. Gastrointestinal disease

1. Pancreatic
2. Subphrenic abscess
3. Intrahepatic abscess
4. Intrasplenic abscess
5. Esophageal perforation
6. Postabdominal surgery
7. Diaphragmatic hernia
8. Postliver transplant

E. Heart disease

1. Postcoronary artery bypass graft surgery
2. Postcardiac injury (Dressler's) syndrome
3. Pericardial disease
4. Pulmonary vein stenosis postcatheter ablation of atrial fibrillation

F. Obstetric and gynecologic disease

1. Ovarian hyperstimulation syndrome
2. Fetal pleural effusion
3. Postpartum pleural effusion
4. Meigs' syndrome
5. Endometriosis

G. Collagen vascular disease

1. Rheumatoid pleuritis
2. Systemic lupus erythematosus
3. Drug-induced lupus
4. Immunoblastic lymphadenopathy
5. Sjogren's syndrome
6. Familial Mediterranean fever
7. Churg-Strauss syndrome
8. Wegener's granulomatosis

H. Drug-induced pleural disease

1. Nitrofurantoin
2. Dantrolene
3. Methysergide
4. Ergot drugs
5. Amiodarone
6. Interleukin 2
7. Procarbazine
8. Methotrexate
9. Clozapine

I. Miscellaneous disease and conditions

1. Asbestos exposure
2. Postlung transplant
3. Postbone marrow transplant
4. Yellow nail syndrome
5. Sarcoidosis
6. Uremia
7. Trapped
8. Therapeutic radiation exposure
9. Drowning
10. Amyloidosis
11. Milk of calcium pleural effusion
12. Electrical burns
13. Extramedullary hematopoiesis
14. Rupute of mediastinal cyst
15. Acute respiratory distress syndrome
16. Whipple's disease
17. Iatrogenic pleural effusions

J. Hemothorax

K. Chylothorax

Symptoms

The symptoms of a patient with a pleural effusion are mainly dictated by the underlying process causing the effusion. Many patients have no symptoms referable to the effusion. When symptoms are related to the effusion, they arise either from inflammation of the pleura, from compromise of pulmonary mechanics, from interference with gas exchange, or on rare occasions, from decreased cardiac output. A pleural effusion associated with pleuritic chest pain indicates inflammation of the pleura, specifically, the parietal pleura as the visceral pleura does not have pain fibers. Some patients with pleural effusions experience a dull, aching chest pain rather than pleuritic chest pain rather than pleuritic chest pain.

Ordinarily, the pain associated with pleural disease is well localized and coincides with the affected area of the pleura, because the parietal pleura is innervated mostly by the intercostals nerves. At times, however, pleuritic pain is referred to the abdomen because intercostals nerves are also distributed to the abdomen. A notable exception to the localization of the pain occurs when the central portion of the diaphragmatic pleura is involved. The nerve supply to this portion of the parietal pleura is the phrenic nerve; therefore, inflammation of the central portion of the diaphragm is referred to the tip of the ipsilateral shoulder.

Pleuritic pain felt simultaneously in the lower chest and ipsilateral shoulder is pathognomonic of diaphragmatic involvement.

A second symptom of pleural effusion is a dry, nonproductive cough. The mechanism producing the cough is not clear, although it may be related to pleural inflammation. Alternately, lung occasions, from decreased cardiac output. A pleural effusions associated with pleuritic chest pain indicates inflammation of the pleura, specifically, the parietal pleura as the visceral pleura does not have pain fibers. some patients with pleural effusions experience a dull, aching chest pain rather than pleuritic chest pain.

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A second symptom of pleural effusion is a dry, nonproductive cough. The mechanism producing the cough is not clear, although it may be related to pleural inflammation. Alternately, lung compression by the fluid may bring opposing bronchial walls into contact, stimulating the cough reflex.

The third symptom of pleural effusion is dyspnea. A pleural effusion acts as a space – occupying process in the thoracic cavity and therefore reduces all subdivisions of lung volumes.

Associated parenchymal disease probably explains this small increase in pulmonary function following therapeutic thoracocentesis. The degree of dyspnea is frequently out of proportion to the size of the pleural effusion. Often, this feature is the result of compromised diaphragmatic function due to the weight of fluid on the diaphragm.

Physical Examination

When the chest of a patient with, or who is suspected of having, a pleural effusion is examined, particular attention should be paid to the relative sizes of the hemithorax will be larger, and the usual concavity of the intercostals spaces will be blunted or even convex. In contrast, if the pleural pressure on the side of the effusion is decreased, as with obstruction of a major bronchus or a trapped lung,

the ipsilateral hemithorax will be smaller, and the normal concavity of the intercostals spaces will be exaggerated. In addition, with inspiratory efforts, the intercostals spaces retract. Enlargement of the hemithorax with bulging of the intercostals spaces is an indication for therapeutic thoracocentesis to relieve the increased pleural pressure. Of course, in many patients with pleural effusions, the hemithoraxes are equal in size and the intercostals spaces are normal.

palpation of the chest in patients with pleural effusions is useful in delineating the extent of the effusions. In areas of the chest where pleural fluid separates the lung from the chest wall, tactile fremitus is absent or attenuated because the fluid absorbs the vibrations emanating from the lung. Tactile fremitus is much more reliable than percussion for identifying both the upper border of the pleural fluid and the proper site to attempt a thoracocentesis. With a thin rim of fluid, the percussion note may still be resonant, but the tactile fremitus is diminished. Palpation may also reveal that the cardiac point of maximum impulse is shifted to one side or the other. With large left pleural effusions, the cardiac point of maximum impulse may not be palpable. In patients with pleural effusions, the position of the trachea should always be ascertained because it indicates the relationship between the pleural pressures in the two hemithorax.

The percussion note over a pleural effusion is dull or flat. The dullness is maximum at the lung bases where the thickness of the fluid is the greatest. As

mentioned earlier, however, the percussion note may not be duller if only a thin rim of fluid is present. Light percussion is better than heavy percussion for identifying small amounts of pleural fluid.

Auscultation over the pleural fluid characteristically reveals decreased or absent breath sounds. Near the superior border of the fluid, however, breath sounds may be accentuated and take on a bronchial characteristic.

This Auscultation of breath sounds does not mean that an associated parenchymal infiltrate is present. Auscultation may also reveal a pleural rub. Pleural rubs are characterized by coarse, creaking, leathery sounds most commonly heard during the latter part of inspiration and the early part of expiration, producing a to-and-fro pattern of sound. Pleural rubs, caused by the rubbing together of the roughened pleural surfaces during respiration, are often associated with local pain on breathing that subsides with breath-holding. Pleural rubs often appear as pleural effusions diminish in size, either spontaneously or as a result of treatment, because the pleural fluid is no longer present between the roughened pleural surfaces.

It is important to realize that an elevated hemidiaphragm can produce all the classic physical findings associated with a pleural effusion. Obviously, the chest is not the only structure that should be examined when evaluating a patient with a

pleural effusion; clues to the origin of the effusion are often present elsewhere. The effusion is probably due to congestive heart failure (CHF) if the patient has cardiomegaly, neck vein distension, or peripheral edema. Signs of joint disease or subcutaneous nodules suggest that the pleural effusion is due to rheumatoid disease or lupus erythematosus (LE). An enlarged, nontender nodular liver or the presence of hypertrophic osteoarthropathy suggests metastatic disease, as do breast masses or the absence of a breast. Abdominal tenderness suggest a subdiaphragmatic process, whereas tense ascites suggests cirrhosis and a hepatothorax. Lymphadenopathy suggests lymphoma, metastatic disease, or sarcoidosis.

Separation of Transudative from Exudative Effusions

The accumulation of clinically detectable quantities of pleural fluid is distinctly abnormal. A diagnostic thoracocentesis should be attempt whenever the thickness of pleural fluid on ultrasound or the decubitus radiograph is greater than 10mm or whenever loculated pleural fluid is demonstrated with ultrasound unless the etiology of the effusions is known. A properly performed diagnostic thoracocentes is takes less than 10 minutes and should cause no more morbidity than a venipuncture. The information available from examination of the pleural fluid is invaluable in the management of the patient.

The transudative pleural effusions develops if the systemic factors influencing the formation or absorption of pleural fluid are altered.

The permeability of the capillaries to protein is normal in the area where the fluid is formed. Example of conditions producing transudative pleural effusions are left the ventricular failure producing increased pulmonary interstitial fluid and a resulting pleural effusion ascites due to cirrhosis with movement of fluid through the diaphragm and decreased serum, oncotic pressure with hypoproteinemia.

In contrast an exudative pleural effusions develop when the pleural surfaces or the capillaries in the location where the fluid originates are altered such that fluid accumulates. The common causes of exudative pleural effusions are pleural malignancy, parapneumonic effusions and pulmonary embolism.

The first question to ask in assessing a patient with a pleural effusions is whether that effusions is a transudative or a exudates. If the effusions is a transudative no further diagnostic pleural procedures are necessary and therapy is directed to the underlying CHF cirrhosis, or nephrotic syndrome. Alternately if the effusion proves to be an exudates a more extensive diagnostic investigation is included to delineate the cause of the effusion.

A pleural fluid of 3gms was used to separate between transudative and exudative using this test misclassified about 10% of pleural effusions. Light

demonstrated the following criteria for diagnosing exudates. Exudative pleural effusions meet the least one of the following criteria.

- Pleural fluid protein divided by serum protein greater than 0.5
- Pleural fluid LDH divided by serum LDH greater than 0.6
- Pleural fluid LDH greater than two thirds of the upper limit of normal serum LDH

In react years following are the other test for the separation of transudative from exudates include pleural fluid cholesterol>60mg, pleural fluid>45mg, pleural fluid serum albumin gradient of <1.2, pleural fluid protein gradient <3.1, pleural fluid serum bilirubin ratio >0.6 indicating exudates. lights criteria identify approximately 20% of transudative effusions. The mislabeling occurs most commonly when patients with CHF are treated with diuretics before thoracocentesis is performed. these mislabeled transudates barely meet the exudative criteria.

The mislabeled transudates can be identifiers by examinations the gradient between the serum and the pleural protein levels. If this gradient is greater than 3.1g/dl, one can presume that the fluid is actually a transudative an albumin gradient of 1.2g/dl rather than the protein of 3.1 g/dl be used. However the protein gradient is equally effective as the albumin gradient.

The following approach is recommended for determining whether a pleural effusion is a transudate or an exudates. First assess the fluid for light criteria. The higher the value for the protein ratio the LDH ratio and the absolute value of the LDH the more likely the fluid is an exudates. If the fluid meets the criteria for an exudative effusion by only a small margin and the clinical picture is compatible with a transudative effusions measure the protein gradient between the serum and pleural fluid. If this value is greater than 3.1 g/dl then the fluid can be relabeled a transudate.

Other Characteristics of transudates

Most transudates are clear, straw colored, no viscid, and odorless. It takes a pleural fluid red blood cell (RBC) count of more than 10,000/mm^3 to give the pleural fluid a pinkish tinge. Approximately 15% have RBC counts this level.

The discovered of blood-tinged pleural fluid does not mean that the fluid is not a transudate. Because RBCs contain a large amount of LDH, one might suppose that the LDH level in a blood-tinged or bloody transudative pleural effusion would be elevated that it would meet the criteria for an exudative pleural effusion.

The pleural fluid white blood cell(WBC) count of most transudates is less than 1,000/mm^3 , but approximately 20% have WBC counts that exceed

1,000/mm^3, pleural fluid WBC counts above 10,000/mm^3, are rare with transudative pleural effusions.The differential WBC count in transudative pleural effusions may be dominated by polymorphonuclear leukocytes, small lymphocytes, or other mononuclear cells . In a series of 47 transudative pleural effusions ,6(13%) had more than 50% polymorphonuclear leukocytes, were as 16(34%) had predominatly small lymphocytes, 22(47%) had predominatly other mononuclear cells and 3(6%) had no single predominat cell type. the pleural fluid glucose level is similar to the serum glucose level, but the pleural fluid amylase level is low. The pleural fluid pH with transudative pleural effusions is higher than the simultaneously obtained blood ph, probably because of active transport of bicarbonate from the blood into pleural space.

Separation of Exudates from Transudatives

If free pleural fluid is demonstrated on the decubitus film, with ultrasound or with a CT scan, one should consider performing diagnostic thoracocentesis. it has been my experience that diagnostic thoracocentes is difficult if the thickness of the fluid on the decubitus radiograph, ultrasound, or the CT scan is less than 10 mm. if the thickness of the fluid is greater than10 mm, however consideration should be given to performing a diagnostic thoracocentesis. if the patient has congestive heart failure, diagnostic thoracocentes is has to be performed if any of

the following three conditions are met: (a) the effusions are note bilateral and comparably sized,(b) the patient has pleuritic chest pain, or (c) the patient is febrile . Otherwise treatment of the congestive heart failure is initiated. if the pleural effusions do not rapidly disappear, a diagnostic thoracocentesis done later. one of the main purposes of the diagnostic thoracocentesis is to determine whether the patient has a transudative or a excudative pleural effusion.

Radiographic Examinations

Pleural effusions

Typical arrangement of free pleural fluid

Two main factors influence the distribution of free fluid in the pleural space. First the pleural fluid accumulates in the most dependent part of the thoracic cavity because the lung is less dense than pleural fluid.

Bearing in mind that the distribution of fluid within the free pleural space obeys the law of gravity and the lung maintains its shape when compressed, it is easy to predict the distribution of the hemithorax and comes to rest between the inferior surface of the lung an the diaphragm, particularly posteriorly, where the pleural sinus is the most inferior. when the fluid accumulation is higher , the fluid

spills out into the costophrenic sinuses posteriorly, laterally, and anteriorly. Additional fluid spreads upward in a mantle like manner sound the convexity of the lung and gradually tapes as it assumes a higher position in the thorax.

In the posteroanterior projection, the lateral costophrenic angle is obliterated. The density of the fluid is high laterally and curves gently downward and medically with a smooth, meniscus- shaped upper border to terminate at the mediastinum. the layer of fluid is narrower at the mediastinal border than at the coastal border. In the lateral projection the upper surface of the fluid density is semicircular, high anteriorly and posteriorly, and curving smoothly downward to its low2est point approximately midway between the sternum and the posterior chest wall.

Frequently a midfle lobe step is observed on the lateral radiograph. the explanation for the middle lobe step is that as pleural fluid accumulates, the first affected lobe is the lower lobe because it is mostdependent. Therefore, it stains to shrink ands float but maintain its shape. The middle lobe is unaffected and maintains its full volume. Accordingly the result is a shruken lower lobe with a middle lobe that retains size. Radiographically, the fluid is mostely i the posterior part of the chest.

on the basis of the radiologic appearance, one might surmise that the height of the plueral fluid is greater laterally. The meniscus shape is seen because the

layer of fluid is of insufficiently depth to cast a discenible shadow when viewed an face.

Radiologic signs

With the patient in the upright position, fluid first accumulates between the inferior surface of the lower lobe and the diaphragm. If the amount of fluid is small, it occpies this position without spilling into the costophrenic sinuses. With this small amount of fluid, the amount of fluid the normal configuration of the diaphram is maintained andf the chest radiograph does not indicate that pleural fluid is present. when more fluid accumulates it spills over into the posterior costophrenic angle obliterates thae sinus as viewed in the lateral projection.The normally sharp posterior costophernic angle is obliterated by a shallow the homogeneous shadow whose upper surface is meniscus -shaped.

The plueral line up the postreior thoraic wall is also widened. Anytime the posterior costophernic angle is obliterated or a posterior part of one aor both diaphrams is diagnostic erfforts be made. Morever,if the both posterior costophernic angle are clear and sharp, the presence of the clinically significant amounts of free plueral fluid can be nearly excluded. Increasing amounts of fluid blunt the lateral costophernic angle of posteroanterior radiograph. as the more fluid

accumulates the entire outline of the diaphram on the affected side is lost and the fluid extends upward around the anterior, lateral and posterior thoraic walls. This fluid produces opacification of the lung base and the typical meniscus shape of the fluid.

Supine position

Three characteristics serve to differentiate the increased density due to pleural fluid from that due to a parenchymal infiltrate.

First if the density is caused by pleural fluid the vascular structures of the lung will be readily visible through the density in a properly exposed film. Any intrapulmonary process that produces a similar density, however, obliterates the vascular structure by the silhouette effect.

Second, if the density is due to pleural fluid, it is usually completely homogenous. In contrast, infiltrates caused by intrapulmonary processes are usually less homogenous.

Third, air bronchograms are present only if the increased density is due to a parenchymal infiltrate.

Ultrasound

Ultrasound can be used in several different situations, including the following: (a) whether pleural fluid is present; (b) identification of the appropriate location for an attempted thoracentasis, pleural biopsy, or chest tube placement; (c)

identification of pleural fluid loculations; (d) distinction of pleural fluid from pleural thickening; (e) semiquantitation of the amount of pleural fluid; (f) differentitation of a pyopneumothorax from a lung abscess; (g) assessment as to whether a pleurodesis is present; and (h) evaluation of the trauma patient for the presence of a hemothorax or a pneumothorax.

Diagrammatic explanation for the meniscus shape of pleural fluid. The distance between the lung and the chest wall is the same around the entire lung. The depth of the fluid when viewed an face AA to CC is not sufficient to increase the radiodensity. More laterally at DD to FF however the X-rays beam passes through more and more pleural fluid so that an increases in density is radiologically evident.

Transudative Pleural effusions

Transudative Pleural effusions occur when the systemic factors influencing the formation and absorption of pleural fluids are altered so that pleural fluid accumulates.

Congestive Heart Failure

Congestive Heart Failure is probably the most common cause of pleural effusion. The reason for the low incidence of pleural effusions secondary to heart failure in most studies is that researches interested in pleural effusions of the origin. The incidence of pleural effusions in patients with CHF is high.

Pathophysiology

In recent years concepts of pleural fluid formation and reabsorption in patients with heart failure have undergone significant modifications. In the past, it was believed that the pleural fluid that accumulated in patients with CHF was due to increased pressure in the capillaries in the visceral or the parietal pleura. These increased pressures were thought to result in an increased entry of fluid into the pleural space from the parietal pleura and a decreased removal of fluid through the visceral pleura according to Straling's equation.

The current theories on pleural fluid formation and reabsorption give as a different entry pathway and a different exit pathway for pleural fluid in patients with CHF.

Currently, it is believed that almost all fluid exits the pleural space through the lymphatics in the parietal pleura rather than by passively diffusing across the visceral pleura. Pleural fluid accumulates in patients with CHF when the rate of entry of fluid into the pleural space exceeds the capability of the lymphatics in the parietal pleura to remove the fluid.

Clinical Manifestations

pleural effusions due to CHF are usually associated with other manifestations of that disease. The patient often has a history of increasing dyspnea on exertion, increasing peripheral edema and orthopnea or paroxysmal nocturnal dyspnea. The dyspnea is frequently out of proportion to the size of the effusion. Physical examinations usually reveals signs of both right sided heart failure with distended neck veins band peripheral edema and left sided heart failure with rales and an S_3 ventricular gallop as well as signs of the pleural effusions.

The chest radiograph almost always reveals cardiomegaly and usually bilateral pleural effusions. CHF is by far the most common cause of bilateral pleural effusions, but if cardiomegaly is not present. 88% of the patients studied had bilateral pleural effusions. The mean volume of pleural fluid in the right pleural space (1,084 ml) was only slightly greater than mean volume of pleural fluid in the left pleural space (913 ml). In the patient with pleural effusions secondary to CHF, mediastinal lymphadenopathy is common.

Diagnosis

If the patient has cardiomegaly and bilateral pleural effusions, is afebrile, and does not have pleuritic chest pain, we initiate treatment of the CHF and observe the patient to determine whether the pleural fluid is reabsorbed. If the effusions do not disappear within a few days we then perform a diagnostic

thoracocentesis.One problem with this approach is that with diuretics the characteristics of the pleural fluid may be change from those of a transudate to those of an exudates.

If the pleural fluid meets exudative criteria but the effusion is thought to be to CHF the serum to pleural fluids protein gradient should be examinated. If the greater is gradient than 3.1 g/dl, the pleural effusion in all probably is due to the CHF and additional diagnostic studies are not indicated. Currently the protein gradient of 3.1 g/dl is preferred to the albumin gradient because the protein gradient is already available when light criteria are measured. Another test that should be considered for established the diagnosis of CHF is measurement of the serum or pleural fluid pro-brain natriuretic peptide (pro-BNP)

Treatment

The preferred treatment of pleural effusion secondary to heart failure is to treat failure with digitalis, diuretics, and after load reduction. If we manage heart failure successfully, the pleural effusion disappears. such treatment effectively manages the pleural effusion in most patients with heart failure.

Occasionally, large pleural effusions cause patients to eb very dyspneic. The removal of 0.5L to 1.0L of pleural fluid from such persons may rapidly relieve the dyspnea. patients with heart failure and large pleural effusions refractory to

treatment sometimes receive symptomatic relief from therapeutic thoracocentesis. I such patients interventions to control the pleural effusions should be considered.

Hepatic Hydrothorax

Pleural effusions occur occasionally as a complication of hepatic cirrhosis. pleural effusions usually occur only when ascetic fluid is present.

Pathophysiology

From the fore going studies , it is evident that the pleural fluid in these patients originates from the ascetic fluid. It is probable that the fluid passes directly into the pleural space though defects in the diaphragm. In the patient with tense ascites and increased intra abdominal pressure the diaphragm may be stretched causing microscopic defects. The increased hydrostatic pressure in the ascetic fluid results in a one way transfer of fluid from the peritoneal to the pleural cavity. In some patients transfer of ascetic fluid across the diaphragm by the lymphatic vessels may be important in the production of the pleural effusion. My experience with the placement of the chest tubes in such patients leads me to believe that the direct movement of fluid is the dominant mechanism. In each instance the placement of the chest tube was followed by rapid (within minutes) diminution in the amount of ascities.

Clinical Manifestations

Patients with pleural effusions from cirrhosis and ascities have clinical pictures dominated by the cirrhosis and ascities. At times these patients develop acute dyspnea in associatiuon with large pleural effusions. Although the pleural effusions may be small to moderate in size they are frequently large and occupy the entire hemithorax. The large effusions occur probably because the diaphragmatic defect permits fluid to from the peritoneal into the pleural cavity until the pleural pressure approaches the peritoneal pressure.

Diagnosis

The diagnosis of pleural effusion secondary to cirrhosis and ascites is usually easy. Both a paracentesis and thoracocentesis should be performed to ascertain that the ascites and pleural fluid are compatible with the diagnosis and do not have high polymorphonuclear cell counts.

The pleural fluid is occasionally blood tinged or is frankly, bloody, but such findings have no significance and are probably due to the patient poor coagulation status. The differential cell count may reveal predominantly polymorphonuclear leukocytes, small, lymphocytes, or other mononuclear cells. Amylase levels should be determined and cytologic examination performed on both fluid specimens to rule out pancreatic ascites or malignant disease.

Treatment

The management of pleural effusions associated with cirrhosis and ascites should be directed toward treatment of the ascites because the hydrothorax is an extension of the peritoneal fluid. The patient should be put on a low-salt diet, and diuretics should be administered. The best diuretic therapy appears to be the combination of furosemide and spironolactone. the initial starting does is 40mg of furosemide and 100 mg of spironalactone. This combination appears to have the optimal ratio for the two diuretics.

Other Causes of Transudative Pleural Effusions

Nephrotic Syndrome

Pleural effusion is common in patients with the nephrotic syndrome. The mechanism responsible for the transudative pleural effusion associated with the nephritic syndrome is probably the combination of decreased plasma oncotic pressure and increased hydrostatic pressure. The diagnostic thorcocentesis should be performed to ascertain that the pleural fluid is indeed a transudate. one should always consider the possibility of pulmonary emboli in patients with the nephrotic syndrome and pleural effusions. Long scan or a CT angiogram should be obtained in all patients with the nephrotic syndrome and pleural effusions. If the lung scan or spiral CT scan is equivocal, evidence of deep venous thrombosis should be sought with venograms ,impedance plethysmograms, or a pulmonary arteriogram. The treatment of the pleural effusions associated with the nephrotic syndrome

should be aimed at decreasing the protein loss in the urine to increase the plasma protein and to decrease the increased extracellular volume. This is best accomplished by administering diuretics in conjuction with a low-sodium diet, angiotensin-converting enzyme inhibitors. Serial therapeutic thoracocentesis should not be performed because they only further deplete the protein stores. In selected individuals who are symptomatic from the pleural effusions one should consider a pluerodesis with a sclerosing agent.

TUBERCULOUS PLEURAL EFFUSION

The development of pleural effusion in a patient with absence of radiologically apparent TB indicates that it would be a sequelae to the primary infection that occurred 6 to 12 weeks before or it may be due to reactivation of TB .

Pathogenesis of tuberculous pleural effusion :

In tuberculous patients there are subpleural caseous focus. Tuberculous pleural effusion occurs due to rupture of the subpleural caseous focus in the lung to the pleural space.

In the development of tuberculous pleural effusion the delayed hypersensitivity plays a major role" .There is clonal expansion of lymphocytes sensitized to the tuberculous protein . Initially the macrophages predominate in the pleural fluid from day 2 to day 6 and then the lymphocytes predominate in the pleural fluid.

It is clear that the delayed hypersensitivity increases the pleural capillaries permeability to protein. There is higher rate of pleural fluid formation due to the increased levels of pleural fluid protein. Also there is increased levels of VEGF, which also increases the permeability. This leads to the accumulation of pleural fluid and development of pleural effusion.

Also there is decrease in the clearance of proteins in the pleural space. This is because of the impedance to the clearance of proteins by the lymphatics as a result of delayed hypersensitivity reactions.

Clinical manifestation:

Patients with pleural TB have symptoms such as fever, dry cough, pleuritic chest pain, and dyspnea.

Physical findings are those of pleural effusion such as dullness to percussion and absence of breath sounds.

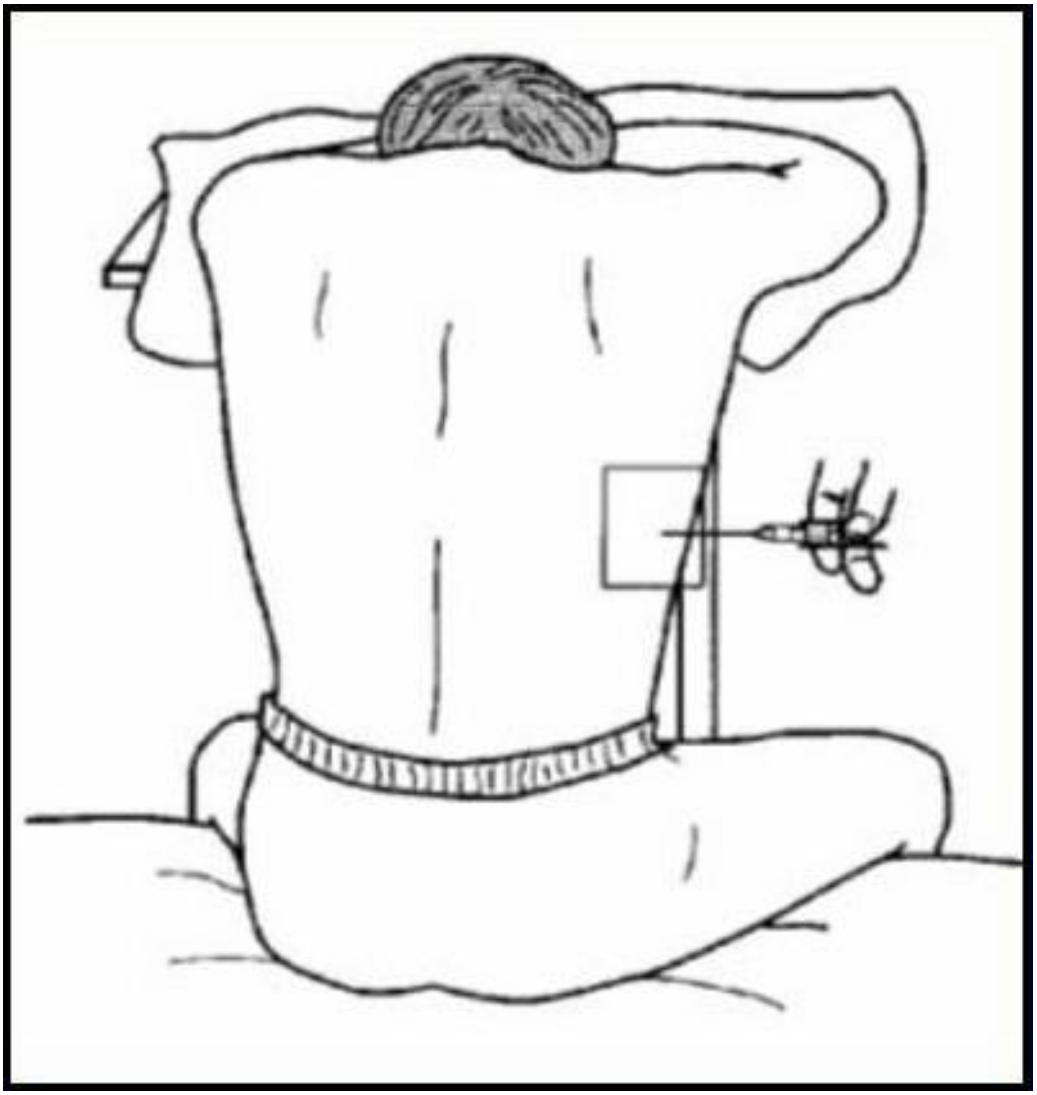
In HIV individuals there will be longer duration of illness. The incidence of chest pain is low, but night sweats, fatigue, diarrhoea, hepatomegaly, lymphadenopathy, splenomegaly are more common.

They have associated parenchymal lesions, smear for acid fast bacilli positive and also culture positive for AFB.

DIAGNOSIS :

Tuberculin skin testing: Tuberculin skin testing is almost always positive if performed after 8 weeks of development of symptoms. So a negative skin testing after 8 weeks of development of symptoms can be used to rule out TB". However in malnourished individuals or HIV patients the test remains negative.

Pleural fluid analysis :



1. Pleural fluid protein elevated and usually above 5 g/dL
2. WBC count has more than 50% small lymphocytes. If there is eosinophils it suggests previous thoracentesis or associated pneumothorax .
3. Mesothelial cells not more than 5 % .
4. Adenosine deaminase levels more than 70 U/L
5. Interferon gamma levels more than 3.7IU/ml

6. Low pleural fluid pH and CRP levels more than 30 mg/dl
7. Pleual biopsy – demonstration of parietal pleura granuloma , AFB , caseous necrosis.
8. Pleual fluid AFB staining and culture for mycobacteria
9. L/N ratio

Parapneumonic effusion:

When any pleural effusion is associated with bacterial pneumonia , lung abscess or bronchiectasis , it is called as parapneumonic effusion.

An empyema is defined as pus in the pleural space. Many complicated parapneumonic effusions are empyema.

According to Weese et al.empyema is characterized by specific gravity greater than 1.018 , protein more than 2.5 g/dL , WBC count more than 500 cells/ mm3 But according to Vianna empyema is defined as pleural fluid protein more than 3.0 g/dL , WBC greater than 15000 / mm3 or positive bacterial cultures.

Pathogenesis:

1. **Exudative stage:**

This stage is characterized by rapid accumulation of sterile pleural fluid in pleural space. The fluid originates from the interstitial spaces of lung and also from the visceral pleural capillaries due to increased capillary permeability. There is low WBC count, low LDH level and a normal glucose level in the pleural fluid at this stage. This stage resolves if appropriate antibiotics is instituted.

2. **Fibro purulent stage**

The pleural space is invaded by the bacteria, if antibiotics are not initiated. In this stage there is accumulation of large amounts of pleural fluids which is rich in bacteria, polymorphonuclear leucocytes and cellular debris. The visceral and parietal pleura are covered by a continuous sheet of fibrin. This leads to the formation of loculation and prevents the spread of pus. But this makes the insertion of chest tube difficult. In this stage there is higher pleural fluid LDH and lower pleural fluid glucose and pH

3. **Organization stage**

This stage is characterized by pleural peel. The fibroblasts grow in to the exudates and an inelastic membrane is produced. The lung is encased by this inelastic pleural peel and makes it functionless. The exudates is thick at this stage and it may spontaneously drain through the chest wall called as empyema necessitants or into the lung producing a bronchopleuralfistula .

The most common organisms are Staphylococcal aureus, Escherichia coli and anaerobe Bacteroids .

Clinical features:

Fever, cough with expectoration, chest pain are the major symptoms .In immune compromised person fever may be absent. If the fever is present for more than 48 hours after the institution of antibiotics then it is called as para pneumonic effusion. The history of alcoholism, seizures or an episode of unconsciousness should be sought as it leads to aspiration.

Light's classification for parapneumonic effusions and empyema :

1. Non significant pleural effusion

2. Typical parapneumonic pleural effusion

3. Borderline complicated pleural effusion

4. Simple complicated pleural effusion

5. Complex complicated pleural effusion

6. Simple empyema

7. Complex empyema”

Diagnosis:

1. During thoracocentesis, there is frank pus.
2. “The pleural fluid will be positive for Gram stain, culture.
3. Pleural fluid glucose less than 40 mg / dL , pH < 7.0 , LDH > 3 times the upper limit.

Also the above findings along with loculations constitutes the bad prognostic factors for both empyema and parapneumonic effusions.

Management:

Antibiotics:

Community acquired pneumonias:

- Fluroquinolones such as levofloxacin, moxifloxacin,gatifloxacin or a macrolide such as azithromycin , clarithromycin plus a beta lactams such as cefotaxime, ceftriaxone, ampicillin – sulbactam.
- If pseudomonas is suspected anti pseudomonas antibiotics like meropenam, imipenam, piperacillintazobactam or cefepime is used.

Anaerobes – metronidazole or clindamycin.

MRSA – vancommycin

Management for pleural effusions:

1. Therapeuticthoracentesis

2. Tubethoracostomy

3. Intrapleuralfibrinolytics like streptokinase , streptodornase , tissue plasminogen activator

4. Video assisted thoracoscopy with lysis of adhesions and / or decortications

5. Decortication

6. Open drinage

ADENOSINE DEAMINASE

Is n enzyme involved in purine metabolism. It is need for the breakdown adenosine from food and for the turnover of nucleic acids in tissues. It is primary function in humans is the development and maintenance of the immune system.

ISOFORMS

There are 2 isoforms of ADA , ADA1 and ADA2,ADA1 is found is most body cells, particularly lymphocytes and macrophages where it is present not only in the cytosol and nucleus but also as the ecto form on the cell membrane.

ADA2 was first identified in human spleen. it was first identified in human spleen. It was subsequently found in other tissues including the macrophage. ADA2 in predominating in the human plasma and serum.

Clinical Significance

ADA2 is the predominant from present in human blood plasma and is increased in many diseases, particularly those associated with the immune system.

Total plasma ADA can be measured using high performance liquid chromatography or enzymatic or colorimetric techniques.

The simplest system in the measurement of the ammonia released from adenosine when broken down to adenosine. After incubation of plasma with a

buffered solution of adenosine the ammonia is reacted with a Berthelot reagent to form a blue color which is proportionate to the amount of enzyme activity.

To measure ADA2,EHNA is added prior to incubation so as to inhibit the enzymatic activity of ADA1.

TB-pleural effusion

ADA can also be used for the workup of lymphocytic pleural effusions. TB pleural effusions can be diagnosed accurately by increased levels of ADA 750perlitre. Low ADA levels essentially excludes tuberculosis from consideration.

Cellular Contents of Pleural fluid

Because of the technical difficulties in obtaining a traumatically access to the normal pleural space the exact volume and cellular content of normal pleural fluid in humans were still unknown.

Using a pleural lavage a technique consisting of injection and immediate aspiration of 150ml of pre warmed saline into the pleural space we were able to determine the total and differential cell count of the few milliliters of original pleural fluid. The extract volume of this original pleural fluid could be measured using area as an endogenous marker of dilution. Expressed per kilogram of body mass, total pleural fluid volume in healthy, non-smoking humans was 0.26/-

0.1ml/kg (-1). Total white blood cells cunt was 1.716 x 10(3) cells me differential cell counts 75% macrophages, 23% lymphocytes, 1.1 mesothelial cells, neutrophils 0.1%, eosinophils 0.1%.

MATERIALS AND METHODS:

Study population:

Patients diagnosed as having pleural effusion on the basis of clinical feature and chest radiography in Government Rajaji Hospital, Madurai over a period of six months will be chosen for the study.

Study design:

Prospective study

Study Period:

Six months between February2016 to July 2016.

Sample Size:

50 eligible cases are studied during this period which fit in for inclusion criteria.

Financial support:

Nil

Conflict of interest:

Nil

Study protocol:

The study is conducted on50 patients with pleural effusion admitted in medical ward grh madurai. Patients will be classified as exudative and transudative pleural effusions based on Light's criteria. All the exudative pleural effusion cases will be studied. Pleural fluid adenosine deaminase levels of > 50U/L[4] will be considered as positive for tuberculous pleural effusion. Pleural fluid Lymphocyte /neutrophil ratio >0.75[4] will be taken as positive for tuberculous pleural effusion. Patients will be treated with antitubercular therapy based on clinical features and pleural fluid analysis and followed up.

The sensitivity, specificity, positive predictive value, negative predictive value for pleural fluid ADA >50 U/L alone and combined pleural fluid ADA and lymphocyte neutrophil ratio of >0.75will be calculated and compared using student t-test.

INCLUSION CRITERIA:

All exudative pleural effusion cases

EXCLUSION CRITERIA:

1. Patients with transudative pleural effusion.
2. Patients with malignant pleural effusion.

3. Patients with immuno deficient states like HIV, those on chemotherapy are excluded.

Data collection:

The study requires the following investigations:

Detailed clinical history

Detailed clinical examination

Blood : Hemoglobin, Total count, Differential count, Erythrocyte sedimentation rate, Random blood sugar, Serum Protein, serum albumin, LDH

Sputum – Acid fast bacilli (Zeihl Neilson staining) .

Chest radiography.

Pleural fluid analysis –

Cells, Protein, Sugar, Gram Staining

-AFB–ZN Staining, Malignant cell cytology

-LDH, ADA, Differential count.

LABORATORY INVESTIGATIONS

Complete hemogram

Renal function test

Liver function test

Sputum AFB, gram stain & culture

Chest x-ray PA view

Pleural fluid analysis

ADA, LDH

-Montoux test

ANTICIPATED OUTCOME:

The combined use of ADA activity and lymphocyte/neutrophil ratio would provide a more efficient means for diagnosing tuberculous pleural effusion than with the use of ADA alone.

STATISTICAL ANALYSIS

Mean and standard deviation for continuous variables and proportions for categorical variables are reported. Ada alone, L/N and ADA values were the combined with various L/N ratios by calculating sensitivity, specificity, PPV, NPV and efficiency. An interactive dot diagram was used for cut-off points and plot versus criteria values graph used. SPSS version 16.0 was used for statistical analysis.

RESULTS AND INTERPRETATION

Table 1 age distribution of the study population (n=50)

Age group	Frequency	Percent
20-40years	20	40
40-60years	25	50
>60 years	5	10
Total	50	100.0

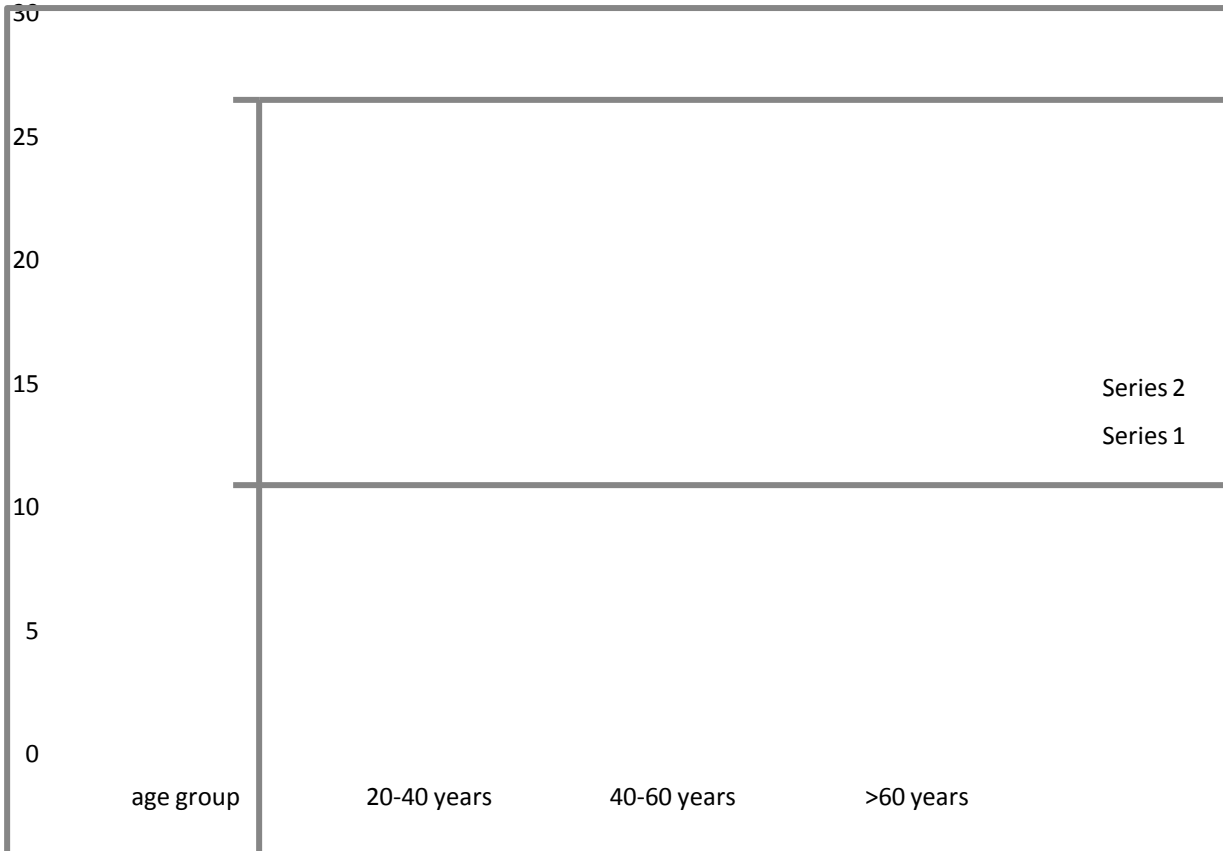


Chart 1 age distribution of the study population (n=50)

Table 2 gender distribution of the study of the population (n=50)

Gender	Frequency	Percent
Female	18	36
Male	32	64
Total	50	100

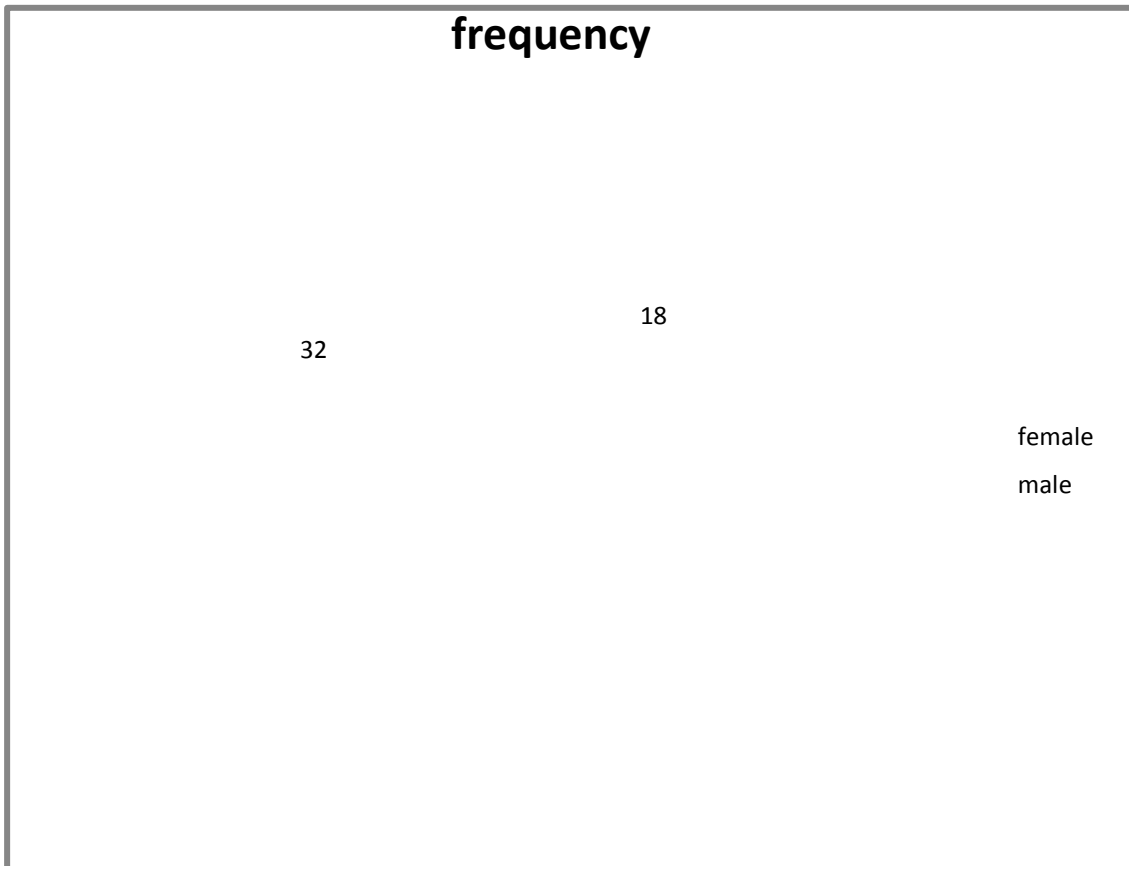


Chart 2 gender distribution of the study of the population (n=50)

Table3 smoker and nonsmoker in study population(n=50)

Pleural effusion	Frequency	Percent
Smoker	28	56
Non-smoker	22	44
Total	50	100

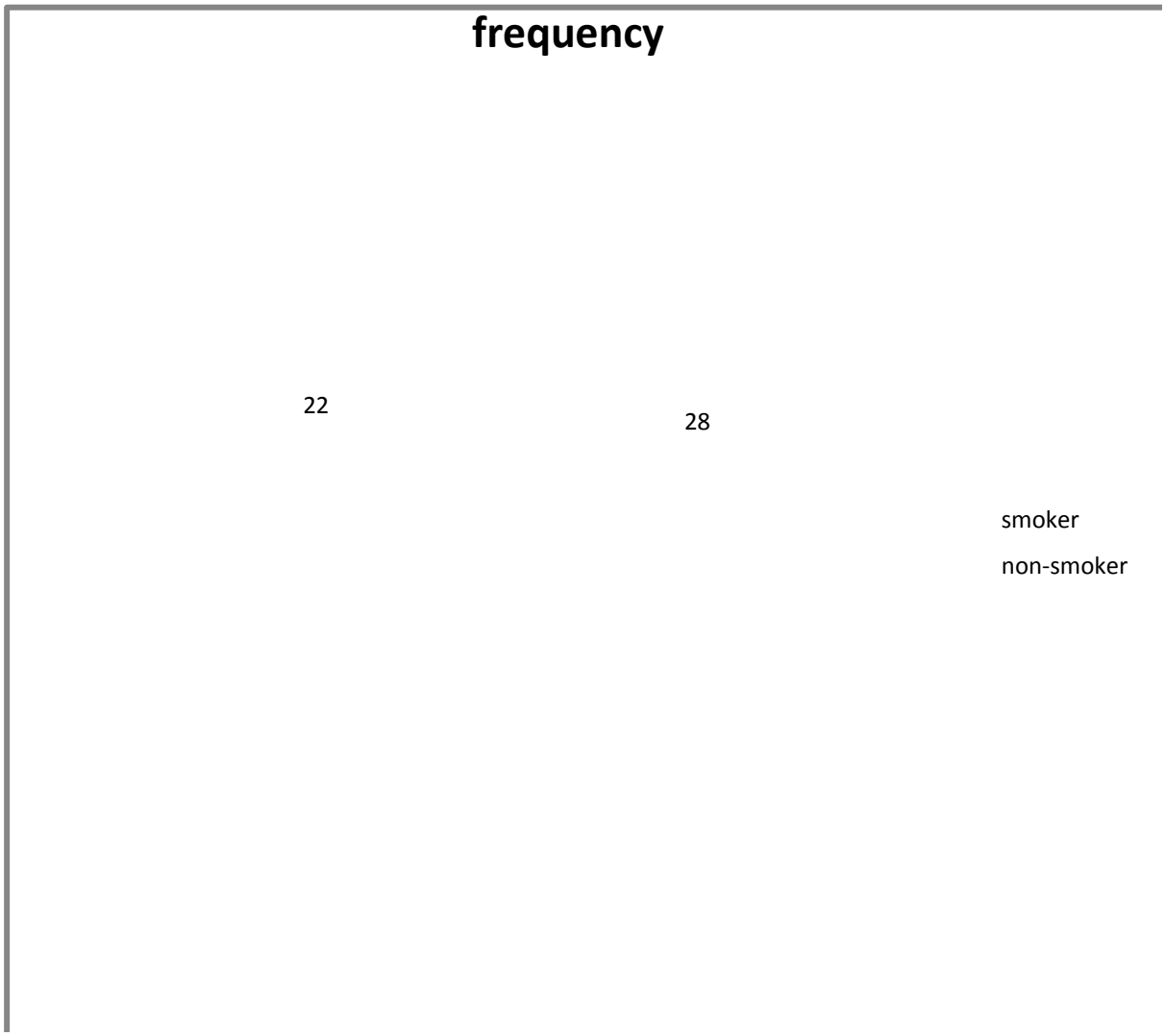


Chart 3 smoker and nonsmoker in study population (n=50)

Table 4 ADA alone (n=50)

ADA alone (U/L)	TB pleural effusion	Non-TB pleural effusion	Total
>50	34	6	40
<50	6	4	10
Total	40	10	50

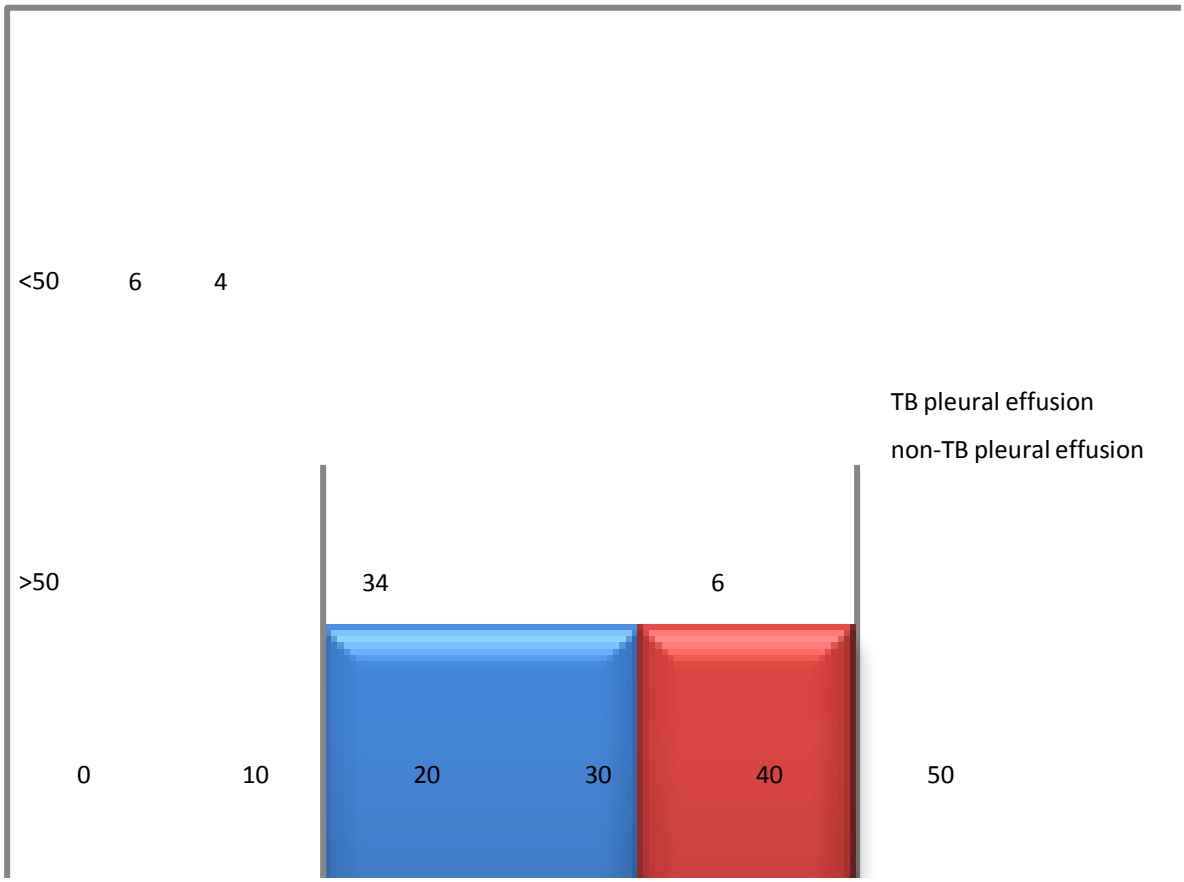


Chart 4 ADA alone (n=50)

Table 5 lymphocyte neutrophil ratio (n=50)

L/N ratio	In TB pleural effusion	Non- TB pleural effusion	Total
>0.75	40	3	43
<0.75	_	7	7
Total	40	10	50

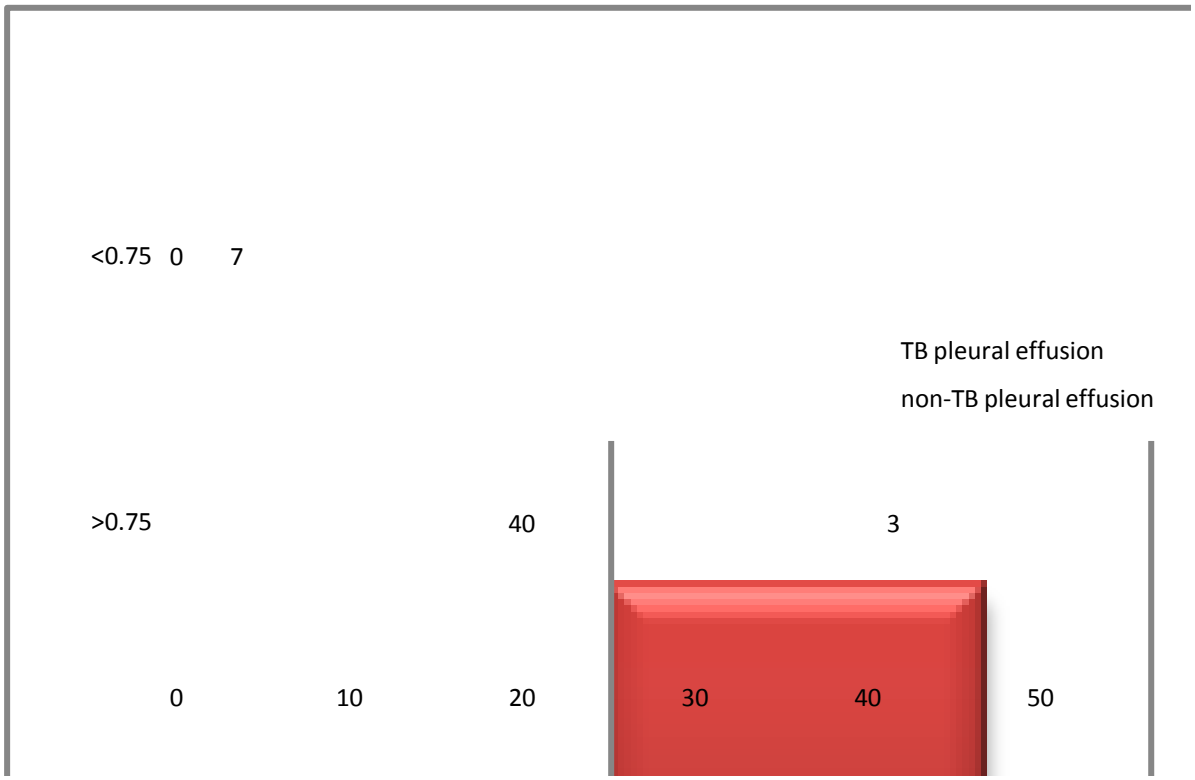


Chart 5 lymphocyte neutrophil ratio (n=50)

Table 6 combined ADA and L/N ratio (n=50)

ADA and L/N ratio	TB pleural effusion	Non-TB pleural effusion	Total
>50 and >0.75	34	2	36
<50 and <0.75	_	11	11
Total	34	13	47

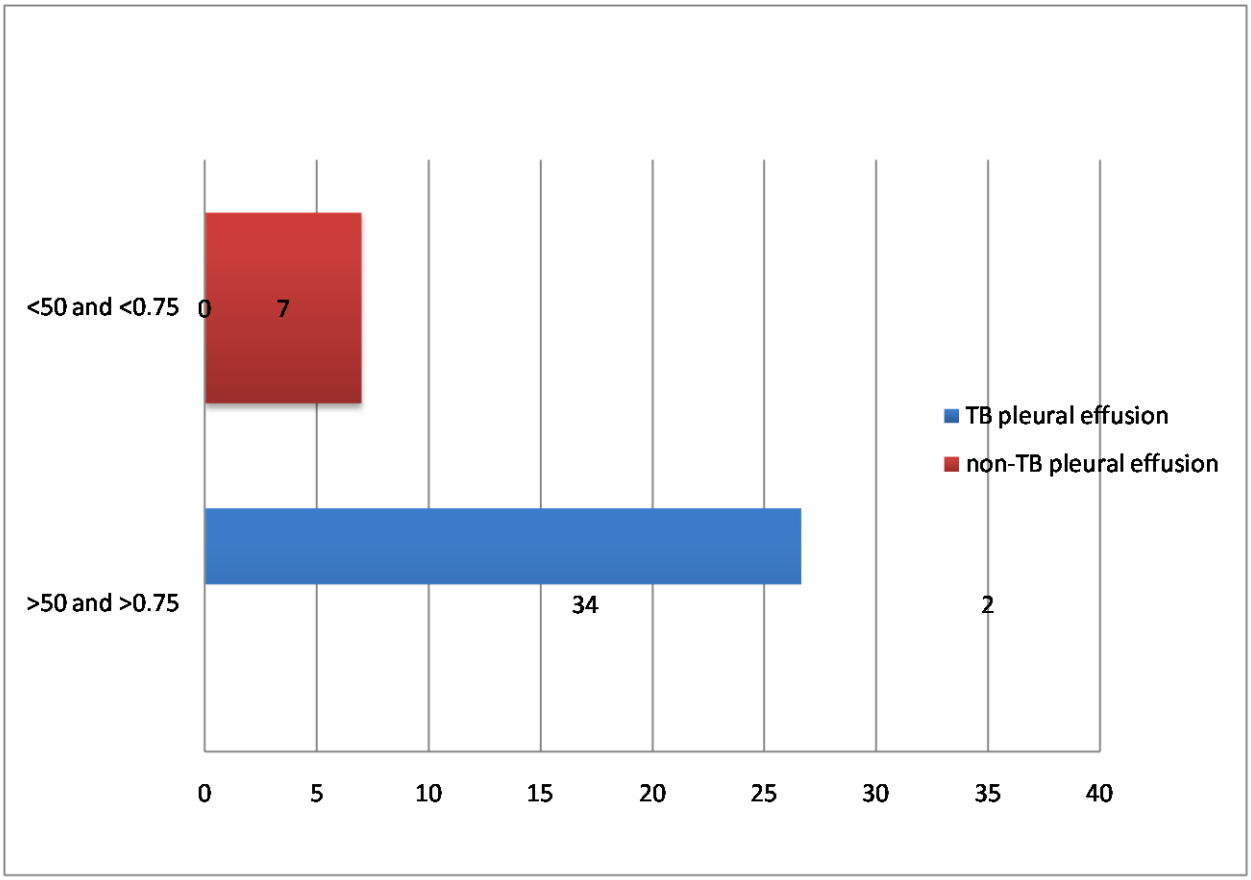


Chart 6 combined ADA and L/N ratio (n=50)

Table 7 criteria used to diagnose TB

“ADA level	L/N ratio	Sensitivity	Specificity	PPV%	NPV%	Efficiency%”
>50U/L	_	61	71	83	45	64
<50U/L	>0.75	100	83	93	100	95
_	>0.75	100	71.4	88.6	100	91.1

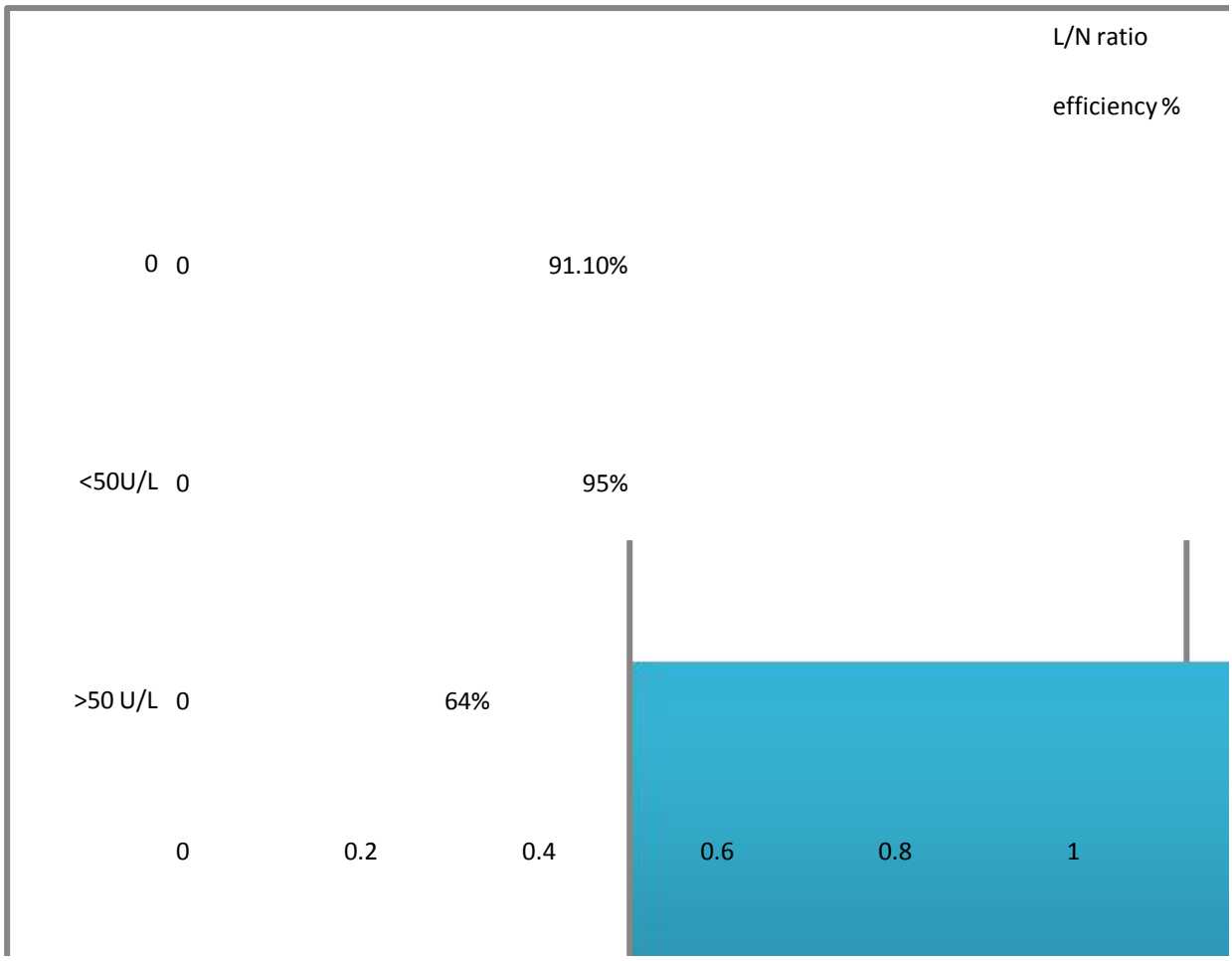


Chart 7 criteria used to diagnose TB

DISCUSSION

Increased ADA activity in pleural effusion is classically associated with tuberculosis. However it may occur due to a number of causes and this may negatively affect the diagnostic utility of ADA measurements and decrease its specificity in the diagnosis of TB. Our results show that, at a cutoff level are 50U/L, ADA has a sensitivity, specificity, PPV,NPV and efficiency of 61%, 71%, 83%, 45%, and 64% respectively. When the L/N ratio's was considered together with ADA activity, the results improved considerably for the diagnosis of tuberculosis pleuiritis. Pleural fluid lymphocytes is also found in malignant conditions, collagen vascular disease, heumaticpleuritis, sarcodosis and up to o third of all transudates. Parapneumonic and empyematous effusions are characterised by neutrophil-predominant, exudative effusions. In the cases and tuberculosis pleurisy, a predominant lymphocyte count was usually found, resulting in a L/N ratio of 0.75 or greater, whereas in other conditions of exudative pleural effusion, L/N ratio was found to be less than 0.75.

TB pleurisy is traditionally diagnosed by either identification of M tuberculosis in pleural fluid and/or biopsy specimen cultures or from the presence granulomas in the pleural biopsy tissue. Pleural fluid cultures have sensitivity of 20-30%, pleural biopsy specimen 50-80%, depending upon the clinician's proficiency. Because of the long culture periods required, clinical and therapeutic decisions are often made before the lab results become available. Polymerase chain

reaction, having a sensitivity of 78% for active disease, has not been found to be an efficient alternative.

CONCLUSION

In conclusion, it is suggested that the combined use of adenosine deaminase activity along with lymphocyte neutrophil ratio would provide a more efficient means for diagnosing tuberculosis pleuritis than the use of ADA alone.

SUMMARY

Increased pleural fluid adenosine deaminase (ADA) activity is classically associated with tuberculous pleuritis. However, increased activity can also occur in a number of other diseases and this may negatively affect diagnostic utility of ADA measurements and decrease its specificity for the diagnosis of tuberculosis.

The presence of ADA in pleural fluid reflects cellular immune response in pleural cavity and in particular, the activation of T lymphocytes. Different disease entities are typically associated with the presence of particular type of leucocytes. The Objectives of the study was to determine whether the combined use of ADA activity and lymphocyte neutrophil ratio would provide a more efficient means for diagnosing tuberculous pleurisy than the use of ADA levels alone.

Biochemistry, cytology and microbiology studies were performed on 50 consecutive pleural fluids. ADA and differential counts were determined on all exudative effusions.”ADA activity in tuberculous effusions was significantly higher than in any other diagnostic group. ADA when combined with lymphocyte neutrophil ratio remains a useful test in the diagnosis of tuberculous pleuritis.

LIMITATIONS OF THE STUDY

1. Pleural fluid cell count in present study was done manually instead of machine and if counting by machine was done it would have been more reliable and accurate.

2. Number of patients studied is small. Small sample size may impede for detecting significant effects because of lack of power.

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PROFORMA

Name:

Age / Sex:

IP no:

Occupation:

Presenting complaints:

Past History:

H/o DM, HT, CVD,CAD,DRUG INTAKE, Thyroid disorders, malignancies pulmonary or extra pulmonary tuberculosis , CLD, COPD.

Personal history

smoker/ nonsmoker

alcoholic/ non alcoholic

Family H/o CKD

Clinical Examination:

General Examination

Vitals:

PR, BP, RR, SpO2

Systemic examination:

CVS, RS, ABDOMEN, CNS

Laboratory investigations:

Complete hemogram, Renal function test ,Liver function test ,Sputum AFB, gram stain & culture, Chest x-ray PA view, Pleural fluid analysis, Urine routine

Diagnosis

ABREVATION

TB-	Tuberculosis
ADA-	Adenosine Deaminase
L/N ratio-	Lymphocyte Neutrophil
LDH-	Lactate Dehydrogenize
AFB-	Acid Fast Bacilli
Non-TB-	Non Tuberculosis

MASTER CHART

S.No	Patient Name	Age	Sex	Diagnosis	Smoker	non - Smoker	ADA U/L	Lympho cyte	Neutro Phil(ml)	L/N Ratio
1	Saravanan	32	M	TB	+	-	60	15	2	> 0.75
2	Senthil	38	M	TB	+	-	70	10	1	> 0.75
3	Lakshmi	26	F	N-TB	-	+	40	0	12	< 0.75
4	Muthu	42	M	TB	+	-	72	10	0	> 0.75
5	Ramaraj	48	M	TB	+	-	82	8	1	> 0.75
6	Mallika	42	F	TB	-	+	100	9	1	> 0.75
7	Palani	62	M	N-TB	+	-	52	2	10	< 0.75
8	Eswaran	63	M	N-TB	+	-	32	1	20	< 0.75
9	Murugeswari	65	F	N-TB	-	+	18	0	8	< 0.75
10	Mani	39	M	TB	+	-	140	10	2	> 0.75
11	Sathyan	28	M	N-TB	+	-	52	3	11	< 0.75
12	Sumathy	37	F	TB	-	+	52	11	2	> 0.75
13	Masilamani	52	M	TB	+	-	118	15	2	> 0.75

S.No	Patient Name	Age	Sex	Diagnosis	Smoker	non - Smoker	ADA U/L	Lympho cyte	Neutro Phil(ml)	L/N Ratio
14	Ramasamy	50	M	TB	+	-	92	12	3	> 0.75
15	Suruliyammal	66	F	N-TB	-	+	56	2	16	< 0.75
16	Sargunam	43	M	TB	+	-	240	10	1	> 0.75
17	Pandian	37	M	TB	+	-	108	12	1	> 0.75
18	Indhirani	36	F	TB	-	+	112	14	2	> 0.75
19	Ponram	48	F	TB	+	-	15	9	0	> 0.75
20	Ramar	46	M	TB	+	-	12	1	9	< 0.75
21	Jothi	44	F	TB	-	+	72	12	2	> 0.75
22	Karuppaiah	35	M	TB	+	-	58	2	10	< 0.75
23	Kumar	24	M	TB	+	-	60	16	2	> 0.75
24	Bhuvana	26	F	N-TB	-	+	23	3	14	< 0.75
25	Andavar	34	M	TB	+	-	64	10	2	> 0.75
26	Arivu	46	M	N-TB	-	+	13	0	22	< 0.75

S.No	Patient Name	Age	Sex	Diagnosis	Smoker	non - Smoker	ADA U/L	Lympho cyte	Neutro Phil(ml)	L/N Ratio
27	Shanthi	47	F	TB	-	+	102	15	3	> 0.75
28	Eswaran	48	M	N-TB	+	-	15	2	19	< 0.75
29	Nagaraj	52	M	TB	+	-	105	16	2	> 0.75
30	Thangam	53	F	TB	-	+	113	9	1	> 0.75
31	Paraman	56	M	TB	+	-	115	8	1	> 0.75
32	Rangasamy	48	M	TB	+	-	9	10	2	> 0.75
33	Saratha	44	F	TB	-	+	68	16	3	> 0.75
34	Miniyappan	50	M	TB	+	-	72	11	0	> 0.75
35	Devanasam	52	M	TB	+	-	76	9	3	> 0.75
36	Lilly	52	F	N-TB	-	+	54	1	7	< 0.75
37	Perumal	58	M	TB	+	-	180	10	2	> 0.75
38	Alagar	36	M	TB	+	-	8	8	3	> 0.75
39	Rathinam	65	F	N-TB	-	+	22	2	10	< 0.75

S.No	Patient Name	Age	Sex	Diagnosis	Smoker	non - Smoker	ADA U/L	Lympho cyte	Neutro Phil(ml)	L/N Ratio
40	Malar	35	M	TB	-	+	56	12	1	> 0.75
41	Selvakumar	32	M	TB	+	-	78	9	2	> 0.75
42	Vijaya	56	F	TB	-	+	84	13	0	> 0.75
43	Kanmani	31	F	TB	-	+	92	8	3	> 0.75
44	Kanagaraj	49	M	TB	+	-	50	10	3	> 0.75
45	Rajamani	57	M	TB	+	-	82	9	2	> 0.75
46	Vishal	22	M	N-TB	+	-	16	3	12	< 0.75
47	Kiruba	24	F	TB	-	+	50	3	10	< 0.75
48	Jegan	32	M	N-TB	+	-	14	2	15	< 0.75
49	Subbaiah	46	M	TB	+	-	68			> 0.75
50	Valli	36	F	N-TB	-	+	38	1	17	< 0.75

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MADURAI, TAMILNADU, INDIA -625 020
(Affiliated to The Tamilnadu Dr.MGR Medical University, Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.R.Suresh
Course	:	PG in MD., General Medicine
Period of Study	:	2014-2017
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	To study the combined use of pleural fluid lymphocyte neutrophil ratio and adenosine deaminase for the diagnosis of tuberculoses pleural effusion
Ethical Committee as on	:	27.07.2016

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

DEAN
Madurai Medical College
Madurai-20

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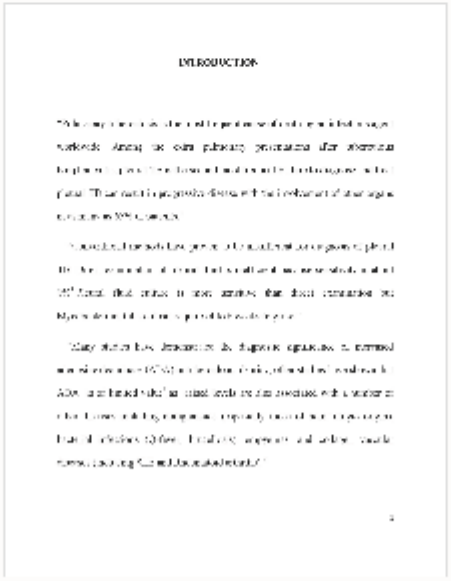

INTRODUCTION

INTRODUCTION

"Pulmonary tuberculosis is the most frequent cause of death by an infectious agent worldwide. Among the extra pulmonary presentations after tuberculous lymphadenitis, pleural TB is the second most frequent Failure to diagnose and treat pleural TB can result in progressive disease with the involvement of other organs in as many as 65% of patients."

"Conventional methods have proven to be insufficient for diagnosis of pleural TB. Direct examination of pleural fluid is inefficient because sensitivity is about 5%[1].Pleural fluid culture is more sensitive than direct examination but Mycobacterium tuberculosis requires 4 to 6 weeks to grow."

"Many studies have demonstrated the diagnostic significance of increased adenosine deaminase (ADA) in tuberculous pleurisy, other studies have shown that ADA is of limited value[2] as raised levels are also associated with a number of other diseases including malignancies (especially those of hematologic origin), bacterial infections (Q-fever, brucellosis), empyemas and collagen vascular diseases (including SLE and Rheumatoid arthritis)."

"Pleural effusions may arise secondary to pulmonary or systemic disease and their development is classically associated with an influx of inflammatory cells into the pleural space. Lymphocytes predominate in malignant and tuberculous pleural effusions[3]."

"Hence this study is aimed to determine whether combined use of pleural fluid lymphocyte neutrophil ratio and ADA activity would provide a more efficient means for diagnosing tuberculous pleurisy than the use of ADA levels."

"Pleural effusion is a very common clinical presentation of diseases. A correct